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LONG-ACTING SULFONAMIDES

The long-acting sulfonamides can be used in place of the short-acting drugs for the treatment of most infections in which sulfonamide therapy is indicated, but they fall far short of measuring up to the claims made for them. These compounds, sulfamethoxypyridazine (Kynex-Lederle; Midicel--Parke-Davis) and sulfadimethoxine (Madribon-Roche), are distinguished by very slow renal excretion. Adequate blood levels of free drug can usually be maintained with a single daily dose, and the total dosage required is much less than that of short-acting sulfonamides. Despite such claims as "90 per cent effectiveness...less than 2 per cent side effects" (Madribon), or "no objective sensitivity reaction, minor subjective reactions also absent" (Kynex), these drugs are still sulfonamides, with most of the limitations as well as the advantages of this class of drugs.

ACTION OF SULFONAMIDES - The antibacterial action of long-acting sulfonamides remains, as with other sulfonamides, primarily bacteriostasis resulting from competitive interference with the utilization of para-aminobenzoic acid by the infecting organism. All sulfonamides have the same range of therapeutic effectiveness, and an organism resistant to one of them is resistant to all. In general, the only significant advantages of long- over short-acting sulfonamides demonstrated so far are convenience of administration and lower cost.

Extravagant claims have been made for the effectiveness of these drugs in wounds and in infections of the respiratory tract, urinary tract and skin. The main objection to these claims is not that they will result in the use of long-acting sulfonamides in place of the short-acting, but that they will encourage the excessive use of sulfonamides. The fact remains that for most infections encountered in practice, penicillin or other antibiotics are preferable to the sulfonamides. Where allergic reactions to penicillin do not preclude its use, that antibiotic is definitely superior to the sulfonamides for the treatment of streptococcal infections. The sulfonamides work more slowly and less effectively than penicillin; when they are used, the streptococcal organism is more likely to persist in the patient, increasing the risk of rheumatic fever or nephritis.

Despite the claims to the contrary, the usefulness of the long-acting sulfonamides, as well as of other sulfonamides, against staphylococcal infections is dubious, and at best very limited. These drugs are not bactericidal, and their bacteriostatic effect is greatly diminished by the presence of pus. In vitro tests

show that only a very small percentage of isolated staphylococcal strains are sensitive to sulfonamides (S.S. Schneierson, J. Mt. Sinai Hosp., 25:52, 1958). Their use in staphylococcal infections is rarely warranted.

AREAS OF USEFULNESS - The sulfonamides are used to treat many urinary-tract infections, but it is not clear at present whether the long-acting drugs with their high blood levels and low urine levels will prove more effective or less effective than other sulfonamides which give much higher levels in the urine for comparable blood levels. However, in one controlled study of the treatment of urinary tract infections with Kynex and Gantrisin, both agents appeared equally effective (B.A. Zikria, et al., Johns Hopkins Hosp. Bull., 103:117, 1958). Most of the organisms which are difficult to eradicate from the urinary tract are resistant to all sulfonamides, long-acting as well as short-acting.

In meningococcus meningitis, sulfonamides remain the therapy of choice. The long-acting preparations give spinal fluid levels no higher than those which follow the proper use of other preparations, however (W. P. Boger, Antibiotic Med., 6:32, 1959). Sulfadiazine has proved eminently satisfactory in wide experience, and the fact that, unlike the long-acting sulfonamides, it can be administered intravenously (as the sodium salt) gives it an important advantage in severe cases of meningococcus meningitis. These same considerations apply to the choice of a sulfonamide for use in conjunction with penicillin in the treatment of pneumococcal meningitis, or with chloramphenicol (Chloromycetin) for H. influenzae meningitis (though some Medical Letter consultants question the advisability of adding a sulfonamide to the antibiotics in these conditions). In Shigella dysenteries, the sulfonamides are generally the drugs of choice, though infections with some strains of the Flexner III and Sonne types have proved refractory.

As already pointed out, sulfonamides should not be used for the treatment of streptococcal infections; their usefulness in prophylaxis against streptococcal infections in rheumatic fever patients is well recognized, however, and once-a-week dosage with a long-acting sulfonamide has been proposed as a means of providing the low blood levels required for prophylaxis (E. Johnson, et al., J. Pediatrics, 54:468, 1959). Monthly injection of a depot form of penicillin (Bicillin-Long-Acting--Wyeth) is the present method of choice in rheumatic fever prophylaxis; the comparative effectiveness of the long-acting sulfonamides remains to be determined. (For a discussion of rheumatic fever prophylaxis, see The Medical Letter, May 15, 1959).

TOXIC AND SENSITIZATION REACTIONS - Neither crystalluria nor serious toxic urinary-tract complications have been reported with long-acting sulfonamides, perhaps because of the much lower urinary concentration of these drugs. But urinary-tract complications of sulfonamide drugs are not common with the rapidly excreted short-acting sulfonamides, such as triple-sulfonamides, sulfisoxazole (Gantrisin-Roche) and sulfadimetine (Elkosin-Ciba); or with sulfadiazine combined with salts which alkalinize the urine. As for other toxic and sensitization reactions (drug fever, skin rash, blood dyscrasias and hepatitis), the long-acting sulfonamides have the same disadvantages as the short-acting drugs. Drug rashes (H.O. Perry and R.K. Winkelmann, JAMA, 169:127, 1959), fatal aplastic anemia (D.R. Holsinger, et al., Proc. Mayo Clinic, 33:679, 1958), severe

Stevens-Johnson disease (J. Salvaggio and F. Conzales, Ann. Int. Med., 51:60, 1959), and toxic hepatitis (W. A. Tisdale, N. E. J. Med., 258:687, 1958) have been reported with the longer-used Kynex. Early reports on Madribon indicate that it is not free from sensitization reactions (H. P. Ironson and C. Patel, Antib. Med., 6:40, 1959, Suppl. 1; J. F. Glenn, et al., ibid., p. 49; J. D. Young, et al., ibid., p. 53). Side effects are minimized when recommended dosages are not exceeded.

The persistence of high levels of free sulfonamide in the blood for days after a single dose of long-acting sulfonamide constitutes a serious disadvantage when sensitization reactions occur. Drug levels are variable with the new drugs, as with the old ones, and the risk of encountering unduly high levels, with their increased toxic and sensitization potential, may be enhanced by slow excretion. The risk is increased in patients with impaired renal function.

If the claim that Madribon has been used by 2,800,000 patients in nine months is accurate, it reflects a failure to realize the limitations of all sulfonamides and underestimation of the toxic and sensitization potential of these drugs; apparently they have been used where no drug is necessary (as in most respiratory infections) and in cases where antibiotics are more likely to be effective.

Madriquid, a reduced-dosage version of Madribon, is offered for those who look askance at "one-a-day dosage." This preparation is obviously irrational, and abandons the special advantage of the long-acting sulfonamides.

The long-acting sulfonamides cost the patient about 20¢ for the daily adult dose of one 0.5-Gm. tablet. The short-acting sulfonamides generally cost about 5 or 6¢ per 0.5-Gm. tablet, but the equivalent daily dosage for systemic infections is 4 or 5 grams, and the comparable daily cost about 40 to 60¢.

ALTAFUR

Furaltadone (Altafur-Eaton) is a nitrofuran which, unlike earlier nitrofurans, is readily absorbed from the gastrointestinal tract. If the claims being made for it are substantiated, it should provide physicians with an important new agent for the treatment of systemic bacterial infections. This new antibacterial chemical is recommended by the manufacturer for the oral treatment of systemic infections caused by staphylococci, streptococci, pneumococci, Esch. coli, and certain other coliform organisms which have shown a high degree of sensitivity to the compound in vitro. The organisms resistant to its action include many strains of B. proteus, B. pyocyaneus and Aerobacter aerogenes.

Altafur is similar in antibacterial activity to the related drugs, nitrofurantoin (Furadantin), which is used for urinary-tract infections (see The Medical Letter, May 29, 1959), and nitrofurazone (Furacin), a topical microbicide. Unlike Furadantin, which gives negligible blood levels and high urine levels, Altafur is claimed to give good blood levels, appearing in the urine only in very low concentrations. According to the manufacturer, it is primarily bactericidal, there is no cross resistance between it and antibiotics, and the development of resistance to it by sensitive organisms has not been observed.

Altafur is claimed to be effective against many bacterial infections - including severe staphylococcal infections - that are resistant to many or even all antibiotics. The drug is also claimed to be relatively free of toxic effects. The manufacturer's investigative studies covered 475 cases in which the drug was used; no independent reports have yet been published. In view of the very limited experience with the drug, reliable judgment both on its therapeutic benefits and on the seriousness and frequency of its allergic, toxic and side effects is not yet possible. The nitrofurans as a group have sufficient potential for serious toxicity, however, to make the use of Altafur in office practice inadvisable at this time. Until well-documented reports from reliable observers support the claims of efficacy and absence of undue hazard, the drug should be considered as still in the investigative stage.

ACID MANTLE CREME

Since the normal skin has a pH of 4.0 to 6.6, the idea of an "acid mantle" that protects the skin from bacterial infection was natural, and the production of an "acid mantle" pharmaceutical agent all but inevitable. Supporting the "acid mantle" idea was the finding that many patients with generalized eczemas and seborrheic dermatoses had high skin pH values in the affected areas (M. Schmid, Dermatologica, 104: 367, 1952), and the further finding that the alkali-neutralizing power of the affected skin was reduced in eczemas (P. Gross, et al., AMA Arch. Derm., 70: 94, 1954).

Acid Mantle Creme and Acid Mantle Lotion (Dome Chemicals) are buffered with aluminum acetate to give the desired acidity. In the study cited above, Gross found aluminum-acetate-buffered cream effective in housewives' eczema. Other authors have reported favorable results when the cream was used as a base for other drugs. None of the published studies showing beneficial effects with "acid-mantle" preparations were controlled, however, and the reports are not convincing.

The claims for Acid Mantle Creme and Lotion rely on the hypothesis that the capacity of the skin to rid itself of harmful bacteria is accounted for to a significant extent by its acidity, and that the maintenance of this acidity is one of the chief aims of clinical management. This "attractive hypothesis" is "largely incorrect," according to D. M. Pillsbury, W. B. Shelley, and A. M. Kligman (Dermatology, W. B. Saunders Co., 1957, p. 122), and the importance of a low pH in antibacterial action on the skin surface is not supported by experimental and clinical data. More significant than pH among the antibacterial mechanisms of the skin are the mechanical keratin barrier, sebum, and sweat (C. T. Nelson and J. T. McCarthy, Med. Clin. of North Amer., 43: 871, 1959).

Among the indications for Acid Mantle Creme or Lotion (in addition to housewives' eczema and many other dermatoses) the manufacturer lists pruritus vulvae and ani (which is usually a neurodermatitis); "athlete's foot" infection; and "dry skin due to various causes." No theoretical or clinical support is given for these indications. Despite the conviction in some quarters of the importance of the skin's "acid mantle," there is no proof of its protective or therapeutic value in skin disorders.

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